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# REVIEW ARTICLE

# Biliary Tree Malignancies: The University of Minnesota Experience

CHUNG K. LEE, MD,[1] BENNET R. BARRIOS, MD,[1] AND HARALDUR BJARNASON, MD[2]
[1]*Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota, Minneapolis, Minnesota*
[2]*Department of Radiology, Section of Cardiovascular and Interventional Radiology, University of Minnesota, Minneapolis, Minnesota*

Because of its slow-growing natural history, most patients with extrahepatic biliary tree malignancies present with inoperable disease. For the minority of patients with operable disease, surgical resection remains the treatment of choice and offers the patient the best chance for long-term local control. The role of chemotherapy and radiotherapy in the management of these patients in the definitive, adjuvant, and palliative setting is expanding, although unsettled. Response rates with chemotherapy have been low and will most likely find a place in a combined multimodality setting. Radiotherapy (external beam, intraoperative, and intraluminal brachytherapy using $^{192}$Ir) has played a major role in the treatment of these cancers. The close proximity of bowel, kidney, and liver limits the external beam radiotherapy doses that can be safely delivered. Since most patients require placement of percutaneous transhepatic biliary catheters to relieve jaundice, this route has been utilized to deliver higher doses of radiation to the tumor area with intraluminal $^{192}$Ir ribbons. The University of Minnesota has treated 15 patients with extrahepatic bile duct cancers. Most were located at the bifurcation of the common bile duct and were treated with intraluminal brachytherapy alone or with external beam radiotherapy. Our results are comparable to previously reported retrospective data with a median survival of 8 months and three long-term survivors.

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**KEY WORDS: radiotherapy; brachytherapy; iridium radioisotopes; biliary tract neoplasms**

## INTRODUCTION

Hepatobiliary malignancies accounted for ~1.5% of all new cancer cases in 1996, with ~2,500 cases of extrahepatic bile duct cancer diagnosed annually [1,2]. These malignancies occur primarily in people between the ages of 50 and 70, with a comparable incidence between males and females [3,4]. Etiologic factors include congenital cystic and dysplastic lesions, intrahepatic calculi, ulcerative colitis, and parasites [4]. Bile duct carcinomas occur 9–21 times more often in patients with ulcerative colitis than the general population [3].

Bile ducts originate in the liver; thus biliary tract cancer can occur anywhere in the hepatobiliary system. Intrahepatic tumors, or ''cholangiocarcinomas,'' arise in the parenchyma of the liver proximal to the bifurcation of the hepatic ducts (only tumors of the intrahepatic bile ducts are considered to be cholangiocarcinomas) [4]. Malignancies of the extrahepatic biliary system include tumors of the gallbladder and the extrahepatic bile ducts

*Correspondence to: Chung K. Lee, MD, Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota, Box 494, UMHC, Minneapolis, MN 55455. Fax: 612-626-7060.
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[5], whereas tumors arising at the bifurcation of the hepatic duct are called Klatskin tumors [6]. Anatomically, the extrahepatic bile duct is divided into three regions. The upper third extends from the right and left hepatic ducts to the common hepatic duct at the level of the cystic duct. The middle third encompasses the entrance of the cystic duct to the intrapancreatic portion of the common bile duct. The lower third runs through the pancreas and wall of the duodenum [2].

This article concentrates on extrahepatic biliary duct malignancies and provides a brief overview of the different treatment options, with particular focus on the role of radiotherapy. In addition, the University of Minnesota experience with inoperable extrahepatic bile duct cancers managed with intraluminal brachytherapy alone or with external beam radiation is discussed.

## DIAGNOSIS AND STAGING

Most bile duct tumors are slow-growing, mucin-producing adenocarcinomas. Over half occur in the upper one-third of the duct. Direct extension to the liver, portal vein, and pancreas is the most frequent route of spread. Lymph node metastases occur in ~40% of all patients. Distant metastases are rare [7,2]. Of the three morphological types (sclerosing, nodular, and papillary), papillary carcinomas have the best prognosis. Papillary and nodular carcinomas usually occur distally around the hilum and in 11% of patients present as a multifocal tumor along the bile duct. In rare cases there is associated profuse intraductal mucorrhea [3].

The most prominent clinical feature is jaundice, which is present in 90–98% of all patients. Because jaundice may be absent in the early stages and complete lobar obstruction may occur without overt signs of jaundice, biliary obstruction should be biochemically tested. High levels of serum alkaline phosphatase, which is the most sensitive biochemical parameter for biliary obstruction, is a good indicator for further investigation of the biliary tract [3,8]. Other clinical features include weight loss, abdominal pain, abdominal mass, and fever. Bacterial infection is also associated with cholangiocarcinomas, especially *Escherichia coli, Streptococcus faecalis,* and *Klebsiella aerogenes* [3,8].

Ultrasonography and computed tomography (CT) scan are useful diagnostic tools to locate an obstruction and evaluate the extent and route of spread [9]. Ultrasound is invariably used for initial screening of patients presenting with jaundice, is cost effective, and is 85–90% accurate in detecting bile duct dilatation. Computed tomography is 90–95% accurate in detecting dilated bile ducts and is better than ultrasound in determining the level and etiology of obstruction [2]. To assess patients with extrahepatic biliary obstruction, percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) are very useful. The latter test has the advantage of providing a pancreatogram, which helps determine the presence of a small carcinoma at the head of the pancreas causing obstruction. The PTC can be used to drain the obstructed biliary tree to achieve partial or complete relief of jaundice. Internal drainage can be achieved by an endoprostheses placed across the malignant obstruction into the duodenum. Along with these tests, celiac and superior mesenteric arteriography with late-phase portography can be used to help determine if the tumor area is resectable. Laparoscopy also is being investigated as a tool to help select patients who are candidates for surgery [9]. Tissue diagnosis should be established through brushings from PTC, ERCP, CT-guided needle biopsy, or open biopsy.

Preoperative staging to determine the level of resectability is critical for optimal treatment. According to the American Joint Committee on Cancer (AJCC), the staging of most extrahepatic bile duct cancers depends on surgical exploration with pathologic examination of the resected specimen as well as on imaging, which defines the limits of the tumor [10]. This staging system is difficult to use for patients who have not undergone surgical exploration because it requires detailed diagnostic data that are obtainable only through surgical observation, such as tumor invasion of the bile duct wall, involvement of surrounding structures and nodes [11]. A staging system proposed by the National Cancer Institute may be applied more broadly and defines stage I as tumor confined to the extrahepatic bile ducts, stage II as involvement of the bile duct and regional lymph nodes, stage III as direct extension to adjacent organs, and stage IV as distant metastases [11].

## OVERVIEW OF TREATMENT AND PATTERNS OF FAILURE

### Surgery

For lesions that can be resected, the endpoint of treatment is cure. Unfortunately, only 20–40% are resectable. Operative procedures for curative intent involve either local excision or hepatic resection. Local excision is indicated for patients in whom preoperative staging suggests no vascular invasion and in whom there are no contraindications to resection. Hepatic resection combined with local resection is indicated in cases with unilobar secondary or tertiary bile duct invasion. Perioperative mortality and morbidity are increased in combined bile duct and liver resection, and survival is about equal to bile duct excision alone. More aggressive resection techniques have been used that suggest an increase in 5-year survival, although these are not standard practice [3].

The location of the lesion appears to be the most important factor in survival after resection. Carcinomas of the lower third of the bile duct are more often resectable and tend to have a higher survival rate than middle or

upper third lesions [12]. Five-year survival rates after resection are 40% in the best prognosis patients and 10% or less in other patients [9].

Tumor recurrence accounts for nearly the total mortality after resection of the extrahepatic bile duct, with 62% of failures in the liver, 42% in the tumor bed, and 20% in the regional lymph nodes. Most patients with a locoregional recurrence develop distant metastasis, although distant disease has been reported to be the first site of failure in 24% of all cases [9].

In the many cases where cure is not possible, operative techniques for palliation include transtumoral or paratumoral drainage and biliary bypass. Transtumoral or paratumoral drainage has been largely replaced by nonoperative percutaneous or endoscopic stenting, which provides permanent expandable metallic indwelling stents. In addition, operative biliary bypass provides palliation for patients with resectable tumors.

## Chemotherapy

The small numbers of patients in most clinical trials do not provide a clear indication for the benefit of chemotherapy to treat these malignancies. Mitomycin C and 5-FU are two single agents that have shown tumor response, although the duration of response has been reported to last only weeks [13]. The average response rate is 16% for single agent regimens and 18% for multiagent regimens. For hepatic artery infusion, the response rates increase to an average of 45% [14].

Chemotherapy combined with radiotherapy may have the potential to increase local control; however, studies have been too small to draw meaningful conclusions. Improved local control with combined radiotherapy and chemotherapy has been suggested by several small nonrandomized studies of patients with pancreatico-biliary cancer [15,16] Gunderson et al. [15] reported a 2-year improvement in survival in patients treated with wide-field external beam radiation and concomitant chemotherapy over patients who received local radiation alone (20% vs. 6.5%, respectively).

## Radiotherapy

Radiotherapy is used for definitive treatment, in the adjuvant setting postoperatively, and for palliation. Many series indicate that radiotherapy improves survival when used as primary treatment for extrahepatic biliary cancer in patients who have not undergone a complete resection [14]. Hayes et al. [17] reported on 24 patients with primary adenocarcinoma of the bile duct (tumors were located between the common hepatic bile duct bifurcation and the ampulla); 14 received definitive courses of radiation (4 by external beam irradiation, 2 by transcatheter irradiation, 8 by both modalities). Median survival was 12.8 months [17]. Mahe et al. [18] reported on 51 patients with carcinoma of the extrahepatic bile duct. The median survival of 12 patients who had an incomplete resection followed by radiotherapy (4 by external radiation alone, 7 by external radiation + $^{192}$Ir, 1 by $^{192}$Ir alone) was 13 months [18]. These studies suggest the median survival of patients treated with definitive courses of radiotherapy (i.e., after biopsy alone) are comparable to those treated with radiotherapy after incomplete resection.

The role of radiotherapy as ''adjuvant'' treatment remains controversial (treatment is considered adjuvant after a potentially curative resection and when there is no evidence of distant metastasis). It is difficult to draw meaningful conclusions regarding its benefit because of the lack of studies examining such things as tumor stage and margin status. These are factors that may affect the outcome of treatment. A benefit is supported by studies that show a significant improvement in survival in patients who received postoperative radiation compared to patients who did not. One study of 17 patients treated with surgery alone and 38 patients treated with surgery combined with postoperative radiotherapy reported a median survival of 8 months and 19 months, and 3-year survivals of 10% and 31%, respectively ($P = 0.0005$). In 51 of these patients, however, there was microscopic tumor infiltration in the resection margins. Only three patients who received postoperative radiotherapy underwent a curative resection [19]. Mahe et al. [18] reported a median survival of 27.5 months for 14 patients who underwent complete gross resection followed by radiotherapy. Microscopic tumor infiltration, however, was noted in 10 of these patients [18].

For advanced bile duct carcinomas with gross or microscopic residual tumor, intraoperative radiotherapy is being evaluated as adjuvant treatment after surgical resection. Intraoperative radiation therapy, during surgical exploration or resection, allows for more precise delivery of radiation to the tumor bed while sparing the normal tissues [14]. Several studies report the use of intraoperative radiation along with other procedures. In a series of 81 patients with bile duct tumors, the survival rates of patients treated by noncurative resection combined with intraoperative radiation (13 patients), biliary drainage with intraoperative radiation (6 patients), and biliary drainage alone (21 patients) were 17%, 20%, and 9%, respectively. Only one patient lived more than 3 years. In another study, intraoperative radiation was combined with postoperative radiation in 12 patients with a median survival of 14 months. Local control in the porta hepatis was achieved in 5 of 10 evaluable patients [14]. Wolkov et al. [20] reported the results of 23 patients with unresected, resected with residual disease, or locally recurrent biliary duct cancer entered on a RTOG phase I–II study. Eight of 23 completed the protocol treatment with intraoperative radiation therapy (IORT). The IORT was delivered with an electron beam to a field that encompassed

all gross disease with a 1 cm margin. External beam radiation therapy was delivered after recovery from surgery. With a median follow-up of 10.5 months, two of eight patients who received IORT are alive.

Intraluminal brachytherapy allows a high dose of radiation to be delivered with relative sparing of the surrounding dose-limiting tissues and organs. Because the effective range of intraluminal brachytherapy is short, it is often used following external beam irradiation as a boost. Combined treatment with external beam radiation and intraluminal brachytherapy is the preferred treatment by many physicians [14]. Several small studies have reported improved results with combination treatment versus either external beam or intraluminal brachytherapy alone [21,14]. Fields and Emami [22] reported on 17 patients with extrahepatic bile duct cancer. Sixteen patients received primary irradiation for unresectable tumors or gross residual tumor after incomplete resection. Eight patients who received $^{192}$Ir in addition to external radiation had improved survival compared to the nine receiving external radiation alone, 15 months vs. 7 months, respectively ($P = 0.06$). A recently published study by Kamada et al. [11] evaluated 145 patients with extrahepatic bile duct cancer treated either by low-dose rate intraluminal $^{192}$Ir irradiation alone, or in combination with external beam radiation. Combined treatment offered a survival advantage for patients not suited for resection as well as for those in whom positive margins were found in the resected end of the hepatic bile duct [11]. A study conducted by the EORTC, however, found no significant improvement in median survival in similar groups of patients, 16.1 months vs. 13.5 months, respectively ($P = 0.38$) [19].

### Dose Response

The optimal dose for the treatment of extrahepatic bile duct cancers has not been established; however, studies suggest that survival is improved with more aggressive radiotherapy. According to Pilepich [23], 45–50 Gy may be necessary to control microscopic disease and 60–70 Gy for gross disease. There has been a trend toward delivering higher doses of radiation to the tumor area, and this has been achieved by combining external beam radiation with IORT or intraluminal brachytherapy. Alden et al. [24] reported a dose response in their cohort of 48 patients treated with external beam irradiation, intraluminal bile duct implant, and chemotherapy. Median survival increased from 4.5 months, 9 months, 18 months, and 25 months with doses of < 45 Gy, 45 to 55 Gy, > 55 to 65 Gy, and 66 to 70 Gy, respectively. Overall, patients achieved a 24-month median survival when doses of > 55 Gy were given, compared with 6 months with doses of < 55 Gy, ($P = 0.0003$). Kamada et al. [11] reported a median survival of 26.2 months in 32 patients treated to a total dose of 70 Gy or more (external beam radiotherapy alone, external beam radiotherapy + intraluminal radiotherapy, or intraluminal radiotherapy) and a median survival of 17.1 months in 27 patients treated with < 70 Gy (the difference did not reach statistical significance). Delivering higher doses increases the risk of damage to normal tissue. Based on the incidence of upper gastrointestinal bleeding in 7 or their 34 patients, Buskirk et al. [25] recommended not using doses in excess of 55 Gy to the stomach or duodenum unless the volumes are small. Weighing the benefit of using doses larger than 55 Gy must take into consideration whether the disease is resectable. If resectable, additional radiation may not be reasonable. If unresectable, a larger dose may be warranted because of the excessive complications resulting from unresected tumor.

### Complications

Possible complications of radiotherapy include fever, radiation-induced hepatic dysfunction, infection and sepsis, obstruction secondary to fibrosis, upper gastrointestinal bleeding, strictures, and gastric and duodenal ulcers. When radiation fields have been limited to the tumor bed and adjacent nodal areas, hepatic-dysfunction is usually not a problem [26]. Alden and Mohiuddin [24] reported more stent-related infections in patients treated with external beam radiation with or without brachytherapy than in patients not given radiotherapy. Mahe et al. [18] found the most common complication to be cholangitis and reported a more frequent incidence of gastric and duodenal ulcers in patients receiving more than 50 Gy. Buskirk et al. [25] reported a 21% incidence of upper gastrointestinal bleeding in 34 patients treated with a minimum of 45 Gy external beam radiation. In a series of 20 patients treated at the Mallinckrodt Institute of Radiology, one patient died of biliary sepsis and another from biliary sepsis attributed to benign strictures [22]. Mogavero et al. [27] reported 7 of 96 patients who required gastrojejunostomy after curative resection or palliative stenting for cholangiocarcinoma involving the hepatic duct bifurcation. This complication was seen only in patients who received radiotherapy (49.6–72.2 Gy).

## MATERIALS AND METHODS

### Patients

Since the early 1980s, 15 patients with inoperable extrahepatic bile duct cancer have been treated in the Department of Therapeutic Radiology-Radiation Oncology at the University of Minnesota. Patients were predominantly female, with only two male patients. The median age was 66 years (range 55–85). All patients except one presented with jaundice. Other common presentations included epigastric discomfort or pain, burning sensation, and poor appetite (Table I).

**TABLE I. Clinical Characteristics of 15 Patients With Biliary Malignancies**

| | |
|---|---|
| Presenting symptoms | |
| Obstructive jaundice | 14 |
| Gastrointestinal symptoms | 12 |
| Weight loss | 5 |
| Sepsis | 2 |
| Histopathology | |
| Well-differentiated adenocarcinoma | 4 |
| Moderately differentiated adenocarcinoma | 6 |
| Poorly differentiated adenocarcinoma | 2 |
| Squamous cell carcinoma | 1 |
| Carcinoid | 1 |
| Not available | 1 |
| Laboratory findings | |
| Serum alkaline phosphatase | |
| Mean | 744 IU/L |
| Range | 317–1518 IU/L |
| Aspartate aminotransferase | |
| Mean | 87 |
| Range | 30–208 |
| Direct bilirubin | |
| Mean | 7.5 |
| Range | 0.1–18.3 |
| Total bilirubin | |
| Mean | 11.3 |
| Range | 0.5–31.8 |

## Diagnosis

All patients had elevated liver function studies, including bilirubin, alkaline phosphatase, and aspartate aminotransferase. Diagnostic procedures included ultrasound in eight patients, ERCP in six patients, abdominal CT in 12 patients, and transhepatic cholangiogram in all patients with catheter placement for intraluminal brachytherapy access. Since most of the patients presented with obstructive jaundice requiring palliative and/or diagnostic drainage of the biliary trees, the treatment of these patients required close collaboration between the Departments of Radiation Oncology and Interventional Radiology.

Ten of 15 patients had exploratory surgery and cholecystectomy, six had common bile duct exploration. A history of gallstones was reported in six of the patients. Pathology reports were available for all patients except one: 12 patients had biopsy proven adenocarcinoma, one patient had a squamous cell carcinoma, and one patient had a carcinoid. In addition, three patients were found to have gall bladder malignancies, two adenocarcinoma, and one adenosquamous cell carcinoma. The most common site of disease was the hepatic bifurcation involving the distal common bile duct and both hepatic ducts. Disease in one patient was predominantly found in the common bile duct and cystic duct. A CT scan or exploratory surgery revealed masses around the duct in seven patients and five patients, respectively. The other patients had more stricture-type lesions. Multiplicity of the tumor was difficult to confirm except for one patient who had obvious multiple lesions. Debulking was attempted in this patient.

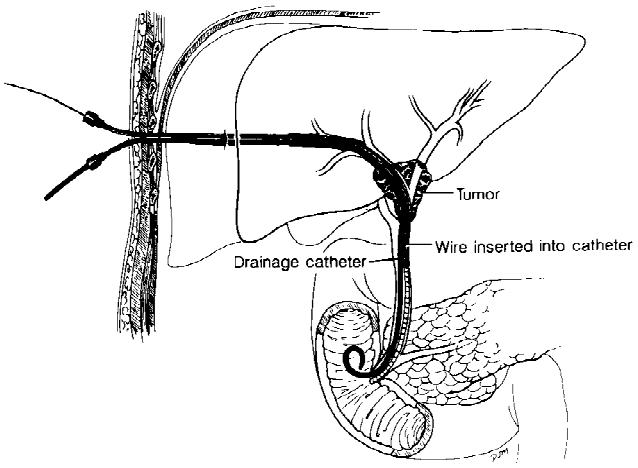


Fig. 1. Percutaneous transhepatic intracanalicular catheter extending from the right biliary system to the duodenum.

## Percutaneous Transhepatic Intracanalicular Catheter Placement

All patients underwent external biliary drainage (which is recommended at least 48–72 hours before $^{192}$Ir implants are placed), and the placement of the intracanalicular catheters was performed by interventional radiology (Fig. 1). If there was involvement of both left and right main ducts as well as the common duct, drains were usually placed percutaneously from both a left and right peripheral duct to the duodenum across the occluded segment. This allowed access to the biliary system proximal and distal to the tumor on both sides. This was important in order to be able to treat the entire extent of the tumor as well as to provide adequate drainage. Appropriate antibiotics were always given prior to any manipulation of the biliary catheters.

Before iridium was placed, a detailed cholangiogram was performed. Films were taken in multiple projections in order to delineate accurately the anatomy of the biliary ductal system and the extent of tumor. Each drainage catheter was then removed over a wire and replaced with two catheters side-by-side. One of the catheters was a drainage catheter. The other was a short 5 Fr angiographic catheter (a 5 Fr Kifa catheter is actually used, which is bought in bulk rolls and cut in short lengths and gas sterilized) with an inner lumen of at least 0.038″. The two catheters were firmly secured to the skin with sutures. A wire was then passed through the 5 Fr catheter at the same time the cholangiogram was performed through the drainage catheter. The distance from the external hub of the 5 Fr catheter to the distal and proximal ends of the tumor was measured with the wire. The measurements were then used to decide the length of the iridium ribbons and how far into the catheter they needed to be placed.

### Radiation Therapy

Twelve of the 15 patients received both external beam irradiation and intraluminal brachytherapy, and all patients receiving external beam radiation were treated with high energy X-rays. Radiation was delivered in fourfield combination to limit dose to the whole or large portion of the liver and kidneys, especially to the left kidney. The total dose was limited because of bowel tolerance. The median dose of external beam radiation was 45 Gy (range 34.5–50.4 Gy) delivered in 25–30 fractions 5 days per week at 150–180 cGy fractions a day.

A total of 19 intraluminal brachytherapy implants were performed in 15 patients using $^{192}$Ir sources. Thirteen of the 15 patients were implanted with two ribbons, one with three ribbons, and one with one ribbon. Four patients had two separate brachytherapy treatments separated by 1–2 weeks. Intraluminal brachytherapy was delivered after external beam radiation. The tumor area and treatment volume were identified by cholangiogram through percutaneous transhepatic catheters used for both biliary drainage and implant access. Antibiotics were given just before any manipulation of the catheters. The catheter was placed by interventional radiology as previously described. The patient was then simulated to verify the placement of the catheter. Dummy sources were loaded to cover the tumor area with a 1–2 cm margin along the ducts. Since the most common site of disease was at the bifurcation of the common bile duct, the ribbons were placed to avoid overlap between $^{192}$Ir sources. When it was not possible to place catheters in both ducts, treatment of the right and left hepatic ducts was divided into two sessions. The dummy and active seed wires were cut to match the length of the tumor and placed into the 5 Fr catheter. Radiographs were taken to verify correct positioning (Fig. 2).

Isodose curves were computer-generated with the dose calculated at a depth of 0.5 cm. Calculations included individual seed activity, inverse square correction from the point source, and tissue attenuation and scatter correction using accepted $^{192}$Ir algorithms. Overlap was avoided at the bifurcation by arranging sources with a 0.5 cm separation between ribbons (Fig. 3). The median dose rate was 58 cGy/hr and the median dose received from the $^{192}$Ir implant was 28 Gy (range 21–35.1 Gy). Three patients treated with brachytherapy only received 25.0 Gy, 28.2 Gy, and 35.1 Gy. Treatment was tolerated well except for short duration anaerobic bacteremia, which occurred in several patients despite antibiotic coverage. After completion of brachytherapy, the 5 Fr and drainage catheters were replaced with a larger drainage catheter. These catheters were left in place indefinitely or replaced with internal stents if desired by the patient. In patients with marked response, the catheters were removed.

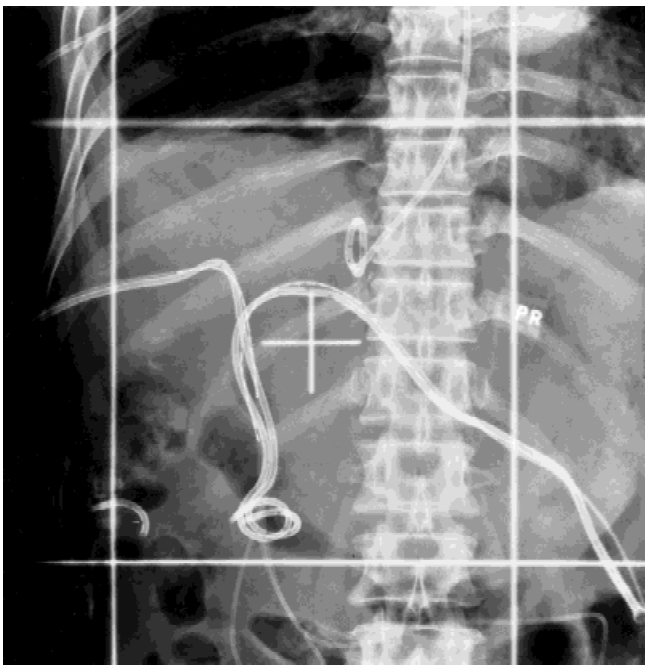

Fig. 2. Radiograph illustrating percutaneous transhepatic intracanalicular catheters placed in the right and left biliary systems loaded with dummy sources to verify $^{192}$Ir placement (isodose distribution shown in Fig. 3).

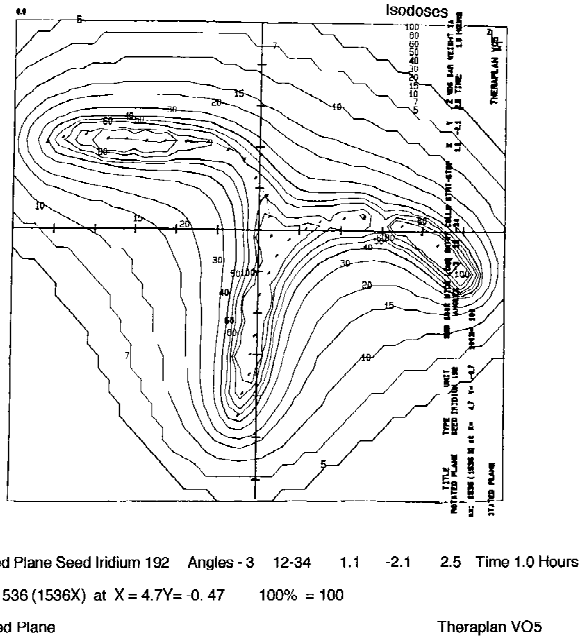


Fig. 3. Isodose distribution of $^{192}$Ir seeds in right and left hepatic ducts (dummy source placement shown in Fig. 2).

## RESULTS

Radiotherapy data for all patients are summarized in Table II. Presently, 12 patients have died of disease 2–95 months after completion of all radiotherapy. Median time

**TABLE II. External Beam and Brachytherapy Doses and Survival of 15 Patients With Biliary Malignancies Treated With Brachytherapy**

| Patient | Age/sex | Site[a] | EBRT (cGy) | $Ir^{192}$ (cGy at 0.5 cm) | Status[b] |
|---|---|---|---|---|---|
| 1 | 56/F | CBD | 4,950 | 3,000 | DwD (88 mo) |
| 2 | 63/F | Bifurcation[c] | 3,450 | 2,750 | NED (148 mo) |
| 3 | 74/F | Bifurcation[c] | 3,600 | 2,835 | DwD (8 mo) |
| 4 | 69/F | Bifurcation[c] | 4,410 | 3,000 | DwD (8 mo) |
| 5 | 68/F | Bifurcation[c] | 4,650 | 2,800 | DwD (4 mo) |
| 6 | 64/F | Bifurcation[c] | 0 | 3,510 | DwD (3 mo) |
| 7 | 55/F | Bifurcation[c] | 4,500 | 3,010 | DwD (10 mo) |
| 8 | 70/F | Bifurcation[c] | 4,200 | 3,200 | DICD (95 mo) |
| 9 | 61/F | Bifurcation[c] | 0 | 2,820 | DwD (36 mo) |
| 10 | 85/F | CBD | 4,500 | 2,805 | NED (24 mo) |
| 11 | 82/F | CBD | 0 | 2,500 | DwD (2 mo) |
| 12 | 62/M | CBD | 5,040 | 3,000 | DwD (4 mo) |
| 13 | 58/M | Bifurcation[c] | 4,500 | 5,500 | DwD (12 mo) |
| 14 | 55/F | Bifurcation[c] | 4,500 | 3,015 | DwD (6 mo) |
| 15 | 79/F | Bifurcation[c] | 4,500 | 2,800 | DwD (8 mo) |

[a]CBD = common bile duct.
[b]DwD = dead with disease; NED = no evidence of disease; DICD = dead of intercurrent disease.
[c]Klatskin tumors.

to death was 8 months (range 2–36 months). Survival was calculated from the time of completion of radiotherapy. The 6- and 12-month actuarial survivals for all patients were 66% and 33%, respectively (Fig. 4). One patient recurred at 60 months and had additional treatment, but died of disease 36 months after retreatment. Three patients died with complications related to treatment, one with sepsis, one with gastrointestinal bleeding, and one with sepsis and gastrointestinal bleeding. Another patient died of congestive heart failure at 95 months without evidence of disease. Two patients are alive at 24 and 148 months.

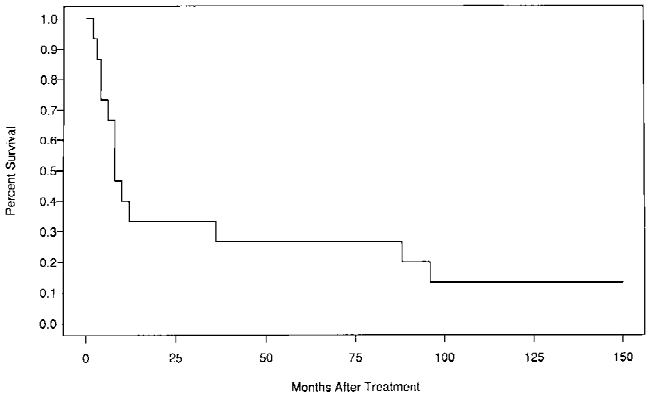


Fig. 4. Kaplan-Meier survival curve.

## CONCLUSION

Biliary tree malignancies are infrequent and difficult to treat. Because of their rarity, large randomized clinical studies have not been conducted to analyze the comparative advantages of treatment options. Despite advances in diagnostic imaging and because of the slow-growing nature of these cancers, early detection is the exception in the majority of these patients. Complete surgical resection remains the primary treatment. The majority of these carcinomas, however, are either unresectable or residual disease remains after attempted resection. Because of the high incidence of gross or microscopic residual disease after surgery, radiotherapy and/or chemotherapy have been used to decrease local recurrence after resection alone and increase median survival.

The role of chemotherapy remains small, with most series showing only minimal improvement. The benefits of chemotherapy in palliation and prolongation of survival are controversial. Response rates from single agent and multiagent regimens are low, although hepatic artery infusion has resulted in response rates averaging as high as 45% [14]. It appears likely that any benefit chemotherapy may have will result from multimodality treatment with radiotherapy, but few studies to date have examined this approach.

Radiotherapy (external beam, intraluminal, or intraoperative) plays a major role in the treatment of these cancers with many small series showing improvement in local control and survival. Hayes reported a median survival of only 2 months in patients treated without definitive radiotherapy. A median survival of 10 months was reported by Mahe et al. [18] for patients treated palliatively (overall survival was approximately 40% at 12 months and 5% at 24 months). In the definitive treatment of these cancers, radiotherapy has resulted in median survivals of ~13 months, and 19–28 months following complete gross resection. The median survival for patients treated at the University of Minnesota are compa-

rable to previously reported retrospective studies, although three of our patients survived 5 years or longer.

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